

Promotion

Although Merck does not intend to encourage the concomitant use of FOSAMAX™ with HRT, we cannot commit to not promote, since this might be interpreted to preclude the use of publications. As discussed with the Agency, Merck wishes to reserve the right to distribute publications (without disclaimers) which contain data based upon the use of FOSAMAX™ with HRT.

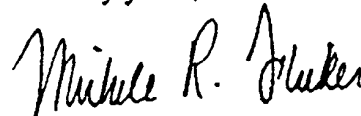
Carcinogenesis Language

MRL proposes that Dr. Steigerwalt's request to modify the existing carcinogenesis language not be discussed at the present time. After Dr. Steigerwalt has had the opportunity to review the data, MRL will work with him to resolve any remaining issues.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Steve Caffé, MD (610-397-2835).

Sincerely yours,



Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Attachments: Fax –November 19, 1999: Mr. Randy Hedin (301-443-9282)
Mockup package circular

Fax/Federal Express

Desk Copy with Attachments: Mr Randy Hedin, HFD-510, Room 14B-04 – Federal Express #1

Michele R. Flicker, MD, PhD, FACP

Merck & Co., Inc.
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November 19, 1999

Solomon Sobel, MD, Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



**NDA 20-560/S-015, S-018: FOSAMAX™
(Alendronate Sodium Tablets)**

AMENDMENT TO PENDING SUPPLEMENTAL APPLICATIONS

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug applications cited above for FOSAMAX™ (Fracture Intervention Trial (FIT), 4-Year Data) submitted September 3, 1998 and FOSAMAX™ (Estrogen/HRT) submitted January 28, 1999. Further reference is made to the Agency's September 3, 1999 Approvable Letter for S-015 and to the November 9, 1999 amendment to this supplemental application. The draft labeling submitted with the November 9, 1999 amendment to S-015 also included the draft labeling for supplement S-018. Reference is also made to the Agency's November 10, 1999 facsimile transmission which requested additional revisions to the draft labeling provided for supplement S-018. Finally, reference is made to the November 18, 1999 teleconference in which the Agency and Merck Research Laboratories (MRL, a division of Merck & Co., Inc.) discussed and resolved all pending S-015 and S-018 labeling issues.

With this submission, MRL is providing a revised package circular and patient package insert which reflect the revisions agreed upon at the teleconference. Key elements of the revised package circular include the:

- Histomorphometry results from S-018 (Estrogen/HRT)
(in response to the November 10, 1999 Agency request)
- Description of the S-015 (FIT-4) study population completion rate
(in response to the September 3, 1999 Approvable letter)
- Adverse event table based on S-015
(in response to the September 3, 1999 Approvable letter)

Because there are many parameters by which bone turnover may be assessed histomorphometrically, MRL believes the second sentence in the histomorphometry paragraph (revised mock-up, p.15) is incomplete without defining the parameter used to generate the percentage values cited for bone turnover suppression. In this case, the parameter was mineralizing surface. Thus, although not yet incorporated into this faxed version of the package circular mockup, MRL plans to add the clarifying phrase "(as assessed by mineralizing surface)" to the second sentence of the above-mentioned histomorphometry results language. The histomorphometry paragraph will then read:

"Histomorphometric studies of transiliac biopsies in 92 subjects showed normal bone architecture. Compared to placebo there was a 98% suppression of bone turnover (as assessed by mineralizing surface) after 18 months of combined treatment with FOSAMAX and HRT, 94% on FOSAMAX alone, and 78% on HRT alone. The long-term effects of combined FOSAMAX and HRT on fracture occurrence and fracture healing have not been studied."

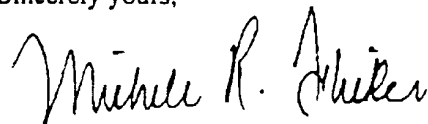
MRL will send a new mockup with this last revision, as well as the clean running text versions of the package circular and patient package insert, on Monday, November 22, 1999.

MRL wishes to express its appreciation to the Agency for a productive and collaborative teleconference.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Steve Caffé, MD (610-397-2835).

Sincerely yours,



Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Q:\daly\Amend1118

Attachments

Fax 18-Nov-1999: Mr. Randy Hedin (301-443-9282)

Michele R. Flicker, MD, PhD, FACP

November 3, 1999

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BEST POSSIBLE COPY

**NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)**

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug application cited above for FOSAMAX™ (estrogen/HRT) submitted January 28, 1999. Further reference is made to a telephone conversation among Mr. Randy Hedin (FDA), Dr. Bruce Schneider (FDA) and Dr. Michele Flicker (Merck Research Laboratories, Inc (MRI), a division of Merck & Co., Inc.) on November 2, 1999. During this conversation, the Agency questioned apparent inconsistencies between the patient numbers presented in Table 34 (pp. 88-89) and the associated text (p. 86, Reference 2) for FACET Protocol 097.

With this submission, MRI addresses the consistency between patient numbers in Table 34 and the associated text. Numerical differences were usually due to patients who may have received x-rays, but for whom the reports were not available to MRI.

We consider the information included in this submission to be a confidential matter, and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining the written permission of Merck & Co., Inc.

We hope this explanation proves helpful and resolves your concerns. Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732 594-1502) or, in my absence, Steve Caffé, MD (610-397-2835).

Sincerely yours,

A handwritten signature in black ink that reads 'Michele Flicker'.

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Michele R. Flicker, MD, PhD, FACP

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October 27, 1999

Solomon Sobel, MD, Director
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Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



**NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)**

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug application cited above for FOSAMAX™ (estrogen/HRT) submitted January 28, 1999. Further reference is made to several telephone conversations among Mr. Randy Hedin (FDA), Dr. James Gebert (FDA), and Dr. Michele Flicker (MRL, a division of Merck & Co., Inc.) on October 15th, 18th, and 20th, 1999. In those conversations the Agency questioned apparent discrepancies between the SAS analysis dataset bone mineral density (BMD) values and the case report form BMD values provided in this supplemental NDA. Of particular concern were lumbar spine and femoral neck values for certain patients from Protocol 072, especially patients with allocation numbers 10 and 13.

With this submission, MRL is providing an analysis of the probable origin of the differences between case report form BMD values and statistical analysis dataset values. Possible sources for these differences include: 1) the use of longitudinal correction factors for all body sites; 2) adjustments in calculating BMD values when there is a prevalent vertebral fracture; and 3) adjustments for missing vertebral, hip or wrist areas in the BMD scans.

We hope this analysis proves helpful and resolves your concerns. Please direct any further requests or questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Steve Caffé, MD (610-397-2835).

Sincerely yours,

A handwritten signature in black ink that reads 'Michele Flicker'.

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

Q:daly\Resp1027

Attachment

Fax/Federal Express #1

Desk Copies: Ms. Julie Rhee, HFD 510, Room 14B-04 - Federal Express #1
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #1
Dr. James Gebert, HFD-715, Room 10B-45 - Federal Express #2

NDA 20-560/S-018: FOSAMAX™ (Alendronate Sodium Tablets)
Response to Request for Information
Possible Sources of Discrepancies Between Case Report Form BMD
Values and Statistical Analysis Dataset BMD Values

There are several possible sources of discrepancies between case report form BMD values and statistical analysis dataset values. These are the use of longitudinal correction factors for all body sites, adjustments in calculating BMD values when there is a prevalent vertebral fracture, and adjustments for missing vertebrae, hip or wrist areas in the BMD scans.

Since its inception, the FOSAMAX clinical development program employed quality control (QC) centers that are blinded to treatment allocation to process bone mineral density data. As the study progresses, bone mineral density scans from investigator sites are sent to the QC centers which evaluates the results of scans prior to submission of data to Merck Research Laboratories. (More details on the role of these centers can be found in our study protocols.) MRL then includes the QC processed data into the study database, and case report form BMD values are generated from this database. Near the end of the trial, the QC center generates longitudinal BMD correction factors which provide an adjustment for measurement drift over time at a study site. The QC center provides MRL with a report that documents the appropriate correction factors. During the preparation of the original treatment NDA, a decision was made to apply these correction factors to the statistical analysis datasets rather than the study database. This adjustment is done in our data setup programs that create SAS datasets from the study database. Thus, the application of correction factors is one source of discrepancy between the statistical dataset BMD value and the case report form value.

For Protocol 072, all investigator sites used Hologic machines. Medical Data Management (MDM, Waltham, MA.) served as the BMD quality control center for this trial. The availability of the correction factors was briefly described in the clinical study report (Section 6f., p. 24) and the longitudinal correction factors can be found in Appendix 4.20 of the same report.

The correction factors were applied in the following manner for this protocol. The Hologic machine indicates the start date for any correction factor for a study site. Thus for each patient at a study site, the date of the BMD scan is compared with the start date of a correction factor for the site. If the date of the scan is after the start date, then the correction factor is applied in a multiplicative manner. This will result in a discrepancy between the statistical analysis dataset value and the case report form value.

EXAMPLE 1.

Consider allocation number 10 in Protocol 072. This patient had a bone mineral density measurement on day 749 (6/5/97). The lumbar spine BMD case report value was 0.762 gm/cm² and the statistical data analysis set value was 0.76517 gm/cm².

A correction factor of 1.00416 was applied to BMD measurements made with the Hologic densitometer at the study center that included patient number 10 for all measurements made from 5/12/97 onwards.

Thus, since the measurement date for this patient was 6/5/97, the multiplicative correction factor was applied. The value of 0.762 now becomes $0.762 \times 1.00416 = 0.76517$ (rounded to 5 decimal places).

There are several other possible BMD adjustments. Lumbar spine BMD values may be distorted if a prevalent fracture exists at lumbar sites L1-L4. Although this is a rare event, in such an instance, the fractured site is not used in the calculation of lumbar spine BMD at all time points (i.e. the data for this vertebra is deleted from all subsequent BMD calculations). Also, the number of vertebrae scanned for an individual may be inconsistent across time and adjustments need to be made. For this situation, data is carried forward from the last recorded value. Unfortunately, these ground rules do not appear to have been provided with the Estrogen Combination submission. The ground rules can be found in Appendix [3.3] of the two-year Protocol 035/037 extension CSR that was previously submitted to the agency. These are reproduced verbatim in the Appendix. These ground rules are a bit complex and the example below will illustrate their use.

EXAMPLE 2.

In Protocol 072, several conventions were applied for allocation number (AN) 13. AN 13 had a prevalent of L2 vertebral fracture and subsequently fractured vertebra L1 on day 420 (6/17/96). Up to day 420, convention one was applied. Her lumbar spine BMD values were recalculated based on her L1, L3, and L4 AREA and BMC information:

$$\text{BMD} = (\text{L1BMC} + \text{L3BMC} + \text{L4BMC}) / (\text{L1AREA} + \text{L3AREA} + \text{L4AREA}).$$

For study days beyond 420 both conventions above were applied. Thus, L1BMC and L1AREA were deleted due to fracture and the last available values of L1BMC and L1AREA prior to Day 420, which was Day 379, were used instead.

Response to Request for Information

Possible Sources of Discrepancies Between Case Report Form BMD Values
And Statistical Analysis Dataset BMD Values

Here is an example of Day 568 (12/19/96). The lumbar spine BMD case report value was 0.825 (gm/cm²) and the statistical analysis dataset value was 0.78842.

	L1	L2	L3	L4
BMC(gm)	7.34*	NA**	12.37	13.79
AREA(cm ²)	11.84*	NA**	14.48	16.17

* : carried forward from Day 379.

** : deleted due to prevalence fracture.

$$\text{Lumbar Spine BMD} = (7.34 + 12.37 + 13.79) / (11.84 + 14.48 + 16.17) = 0.78842$$

APPEARS THIS WAY
ON ORIGINAL

APPENDIX: BMD GROUND RULES

The ground rules for handling fracture vertebra and missing vertebra are reproduced below verbatim from Appendix [3.3] of the two-year Protocol 035/037 extension CSR that was previously submitted to the agency.

Situation: Vertebrae are fractured

Convention: If a vertebra was fractured, all BMD measurements of that vertebra occurring after the time-point of fracture were deleted. For lumbar spine, BMD was re-computed based on the remaining vertebrae measured. Since this deletion would result in inconsistent vertebrae being scanned over time, the following data handling convention would also apply:

Situation: Vertebrae scanned over time are inconsistent

Convention: If the number of vertebrae used to calculate PA lumbar spine was inconsistent over time in the baseline relative day range, then the last value in the range was considered the baseline value, rather than the average of values in the baseline day range.

If the number of vertebrae used to calculate PA lumbar spine was inconsistent over time in the on-treatment portion of the study, previous on-treatment vertebral area, bone mineral content, bone mineral density measurements were carried forward if this would provide consistency over time.

(In addition, for hip and wrist BMD measurements, if the same side of the hip (left vs. right) or the same wrist (left vs. right) were not measured over time, then all measurements not consistent with the baseline measurement were deleted.)

APPEARS THIS WAY
ON ORIGINAL

DESK COPY

RANDY H.

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October 1, 1999

Solomon Sobel, MD, Director
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5600 Fishers Lane
Rockville, Maryland 20857



NDA 20-560/S-018: FOSAMAX™ (Alendronate Sodium Tablets)

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the pending supplemental new drug application cited above for FOSAMAX™ (estrogen/HRT) submitted January 28, 1999. Further reference is made to a September 10, 1999 telephone conversation between Dr. James Gebert (FDA) and Dr. Michele Flicker (MRL, a division of Merck & Co., Inc.) in which Dr. Gebert indicated that the SAS program supporting this supplement was not yielding accurate lumbar spine results as compared to the submitted table 18 for protocol 097 (located in volume 4, published page number 321).

By desk copy with CD to Dr. Gebert, we are providing the corrected SAS datasets and programs.

We apologize for any inconvenience this may have caused. Please direct any questions to Michele R. Flicker, MD, PhD (732-594-1502) or, in my absence, Larry P. Bell, MD (610-397-2310).

Sincerely yours,

A handwritten signature in black ink that reads 'Michele R. Flicker'.

Michele R. Flicker, MD, PhD
Director
Regulatory Affairs

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Federal Express #1

Desk Copy with CD: Dr. James Gebert, HFD-715, Room 10B-45 - Federal Express #2

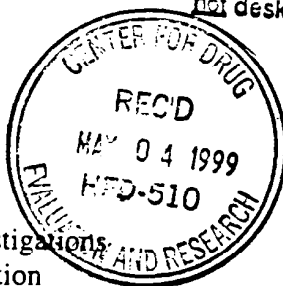
Desk Copy (Letter Only): Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #1

DUPLICATE

NDA SUPP AMEND
SE8-018/BM

Three copies are OFFICIAL FDA COPIES
not desk copies.

May 3, 1999



H.W. Ju, M.D.
HFD-344, Room 125
Division of Scientific Investigations
Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

**NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)
Response to FDA Request for Information**

Dear Dr. Ju:

Reference is made to the pending supplemental new drug application cited above and to an April 16, 1999 telephone conversation between Dr. H.W. Ju (FDA) and Dr. Michele Flicker (MRL, a Division of Merck & Co., Inc.). During this conversation, MRL was informed that the FDA intended to perform inspections at sites 072-012 (Dr. Clark McKeever), 097-007 (Dr. Mark T. Ettinger) and 080-003 (Dr. Robert Jaffe). To facilitate these inspections, the Agency requested additional relevant clinical and monitoring information described below.

With this letter, MRL is providing the requested information. The site-specific clinical information consists of four volumes, two for Dr. McKeever's site, and one each for Dr. Ettinger's site and Dr. Jaffe's site as noted above. The site-specific information for each investigator includes the following:

- Form 1572 for the principal investigator
- Copy of the protocol
- Cover letter used in the past to communicate and summarize changes for each protocol amendment
- Total # patients entered for that investigator
- Total # patients completed
- Total # dropouts and reason for each dropout
- List of protocol violators and associated explanations
- Data listing for adverse reactions
- Primary individual efficacy data listings (listings which were submitted to the NDA)
- Case Report Forms (see next page)

For the Case Report Forms (CRF) section, the list of allocation number enrollment precedes the CRFs. CRFs were requested for the following:

- For site 072-012, the CRF for the 1st, 20th, 40th, and 65th patient enrolled
- For site 097-007, the CRF for the 1st, 10th, 20th, and 35th patient enrolled
- For site 080-003, the CRF for the 1st, 5th, 10th, and 13th patient enrolled

During our preparation of the above materials, three subjects were identified who are not reflected in the final study database. One of those subjects is from study 080-003; the other two from study 080-005. The patient from study 080-003 is the only patient who actually received study drug. Her inclusion in that study report would have influenced the number of subjects enrolled (N = 14 rather than 13 at that site), the number dropped (N = 1 rather than 0 at that site) and possibly the listing of adverse events and protocol violators (N = 2 rather than 1). The primary efficacy analysis per protocol and the conclusions of the study would remain unchanged.

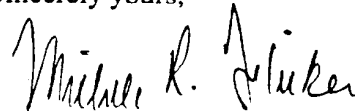
Because these three patients are not included in the final database, additional explanatory information has been attached to the front of the first study 080 volume.

Additionally, we are attaching the two copies of the Monitoring Survey as requested. The Monitoring Survey consists of three sections which are as follows:

- Section I – List of Clinical Studies
- Section II – Monitoring Organizations
- Section III – Standard Operating Procedures

If you have any questions or need further information, please contact Michele Flicker, M.D., Ph.D. (610-397-3193) or, in my absence, Larry P. Bell, M.D. (610-397-2310).

Sincerely yours,



Michele R. Flicker, M.D., Ph.D.
Director
Regulatory Affairs

Attachments

Federal Express #1

Desk Copies (letter only):

NDA 20-560, HFD-510, Room 14B-04 -Federal Express #2

Mr. Randy Hedin, HFD-510, Room 14B-04 -Federal Express #2

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Tel 610 397 2905
Fax 610 397 2516

March 24, 1999



H.W. Ju, M.D.
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Food and Drug Administration
7520 Standish Place
Rockville, Maryland 20855

**NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)
Response to FDA Request for Information**

Dear Dr. Ju:

Reference is made to the pending supplemental new drug application cited above and to a March 17, 1999 telephone conversation between Dr. H.W. Ju (FDA) and Dr. Larry Bell (MRL, a Division of Merck & Co., Inc.) in which you requested additional information regarding clinical studies contained in this supplement. Further reference is made to a March 22, 1999 voice mail message from you to Dr. Bell in which further clarification was made as to the information to be provided. With this submission, we are providing the requested information as follows:

Tab A: Protocol 072:

- 1) The Title page (indicating the full title and protocol number)
- 2) Appendix 3.4 of the Protocol 072 Clinical Study Report which includes the complete investigator list, noting the full address of each site and the number of patients enrolled
- 3) Table A: Patient Listing of Adverse Experiences (production table)

Tab B: Protocol 097:

- 1) The Title page (indicating the full title and protocol number)
- 2) Appendix 3.5 of the Protocol 097 Clinical Study Report which includes the complete investigator list, noting the full address of each site and the number of patients enrolled
- 3) Table B: Patient Listing of Adverse Experiences (production table)

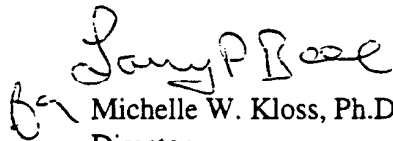
Tab C: Protocol 080 (Non-Alendronate Clinical Pharmacology Study):

- 1) The Title page (indicating the full title and protocol number)
- 2) Appendix 3.4 of the Protocol 080 Clinical Study Report which includes the complete investigator list, noting the full address of each site and the number of patients enrolled
- 3) Table C: Patient Listing of Adverse Experiences (production table)

Additionally, we are attaching Volume 2 of the supplement as you requested. Volume 2 contains the Synopsis of Application.

Please direct any questions to Michelle Kloss, Ph.D. (610-397-2905) or, in my absence, Larry P. Bell, M.D. (610-397-2310).

Sincerely, yours,


for Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

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Attachments

Enclosure (Volume 2 of NDA 20-560/S-018)
Federal Express #1

cc w/attachments:

Solomon Sobel, M.D., HFD-510, Room 14B-04 - Federal Express #2
Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #2

**APPEARS THIS WAY
ON ORIGINAL**

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

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March 1, 1999



Solomon Sobel, M.D., Director
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Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857



**NDA 20-560/S-018: FOSAMAX™
(Alendronate Sodium Tablets)**

Response to Request for Information

Dear Dr. Sobel:

Reference is made to the supplemental new drug application cited above for FOSAMAX™ that was hand delivered on January 28, 1999. Further reference is made to a February 24, 1999 telephone call from Mr. Randy Hedin (FDA) in which he indicated that the Medical and Statistical review copies (Items 8 and 10, respectively) could not be found. Mr. Hedin requested that MRL (a Division of Merck & Co., Inc.) resubmit the Medical and Statistical review copies to the Agency.

By desk copy with attachments to Mr. Hedin, we are providing the requested review copies.

Please direct any questions to Michelle Kloss, Ph.D. (610-397-2905) or, in my absence, Larry P. Bell, M.D. (610-397-2310).

Sincerely yours,

A handwritten signature in dark ink, appearing to read "Michelle W. Kloss".

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Q:\carnal\mk-0217\responses\018_res

Federal Express

Desk Copy with Attachments:

Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express

Larry P. Bell, M.D.
Senior Director
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February 5, 1999

These copies are OFFICIAL FDA COPIES
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Solomon Sobel, M.D., Director
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Central Document Room
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Center for Drug Evaluation and Research
12229 Wilkins Avenue
Rockville, MD 20850

SUPPL NEW CONRESP

SEB-018
SIL



MERCK
Research Laboratories

Supplemental New Drug Application

NDA 20-560 FOSAMAX™ (Alendronate Sodium Tablets)

By copy of this letter, Merck Research Laboratories (MRL) is providing one (1) Compact Disk (CD) which contains the supplemental New Drug Application (sNDA) for NDA 20-560 FOSAMAX™ (Alendronate Sodium Tablets), submitted in hardcopy on January 28, 1999.

This supplemental application provides clinical efficacy and safety documentation for FOSAMAX™ when taken in combination with estrogen/hormone replacement therapy (i.e., estrogen with or without progestin).

The information on this CD [redacted] is to be copied to the StorageWorks Building Block (SBB) [redacted] currently installed on the MRL-dedicated network server in use at the Agency for the Glucocorticoid-Induced Osteoporosis Supplemental New Drug Application disk labeled MK217G electronic submission

A list of reviewers from the Metabolic & Endocrine Drug Products Division and Division of Biometrics who should be provided access to this electronic submission from their desktops may be obtained from Mr. Randy Hedin, Project Manager.

Please notify MRL's Regulatory Agency Relations (RAR) Office (301/881-9000) when the disk installation is successfully completed and access from the reviewers' desktops is functional.

When an action has been taken on this submission and the CD is no longer needed, MRL will make arrangements to retrieve it from the FDA. We understand that, in the future, information submitted in electronic form may be retained indefinitely by the Agency, as an archival copy of the application, in the event that a complete paper submission is not filed.

We have taken precautions to ensure that any software on the CD is free of computer viruses and we authorize the use of anti-virus software, as appropriate.

There are five attachments to this letter:

- Attachment 1 An NDA Table of Contents of the accompanying electronic submission.
- Attachment 2 A Difference Report identifying differences between the electronic version of this submission and the hard copy submission.
- Attachment 3 Installation Instructions detailing how to copy the contents of the CD onto the server.
- Attachment 4 Documentation regarding the development procedures performed at MRL for this electronic submission.
- Attachment 5 A complete list of file names.

During the time that the electronic submission is actively being used, MRL will provide technical support. Any questions relating to this electronic submission should be addressed to me (610/397-2310) or, in my absence, Margo Herron (301/881-9000).

Sincerely,

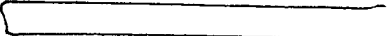


Larry P. Bell, M.D.
Senior Director
Regulatory Affairs

Q:\carnal\mk0217\estrogen\eleccov

Attachments

Enclosures:

Compact Disk (CD)  1

Federal Express #1

cc (cover letter only):

K. Edmunds, Division of Technology Support Services Staff, HFD-70 Federal Express #2
S. Sobel, M.D. HFD-510, Room 14B-04, Federal Express #3
R. Hedin, R. Ph. HFD-510, Room 14B-04, Federal Express #3

cc (cover letter with attachments):

NDA 20-560, HFD-510 (2 copies), Federal Express #4

Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

SEP
5/018

Merck & Co., Inc.
P.O. Box 4, BLA-20
West Point PA 19486-0004
Fax 610 397 2516
Tel 610 397 2905
215 652 5000

DESK COPY

January 28, 1999



Solomon Sobel, M.D., Director
Division of Metabolism and Endocrine Drug Products
HFD-510, Room 14B-04
Office of Drug Evaluation II (CDER)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA 20-560: FOSAMAX™ (Alendronate Sodium Tablets)

Supplemental New Drug Application

Dear Dr. Sobel:

Pursuant to Section 505(b) of the Federal Food, Drug, and Cosmetic Act and in accordance with 21 CFR 314.70 (b), Merck Research Laboratories (MRL) is submitting a Supplemental New Drug Application (sNDA) for FOSAMAX™ (alendronate sodium tablets).

This supplemental application provides clinical efficacy and safety documentation for FOSAMAX™ when taken in combination with estrogen/hormone replacement therapy (i.e., estrogen with or without progestin). The contents of this application include complete Clinical Study Reports for a clinical pharmacology study and two clinical studies as well as a comprehensive Clinical Summary. Draft labeling text is also provided which incorporates the revisions supported by this application.

This application is formatted as required in Title 21, paragraph 314.50 of the Code of Federal Regulations. It consists of a complete "archival" copy (blue binders), comprising 28 volumes, and review copies for each of the two (2) technical sections (one technical review copy for each Item) as described in the Statement of Organization, which is attached to this letter.


In accordance with the Food and Drug Administration Modernization and Accountability Act of 1997 (FDAMA); User Fee I.D. No. [] was sent to the Mellon Bank, Three Mellon Bank Center, 27th Floor (FDA 360909), Pittsburgh, PA 15259-0001, on January 18, 1999.

Merck is requesting a categorical exclusion from the requirements to prepare an Environmental Assessment for this supplemental application under 21 CFR §25.31(a). The supplement meets the requirements of a categorical exclusion under 21 CFR §25.31(a) because it will not increase the use of the active moiety, alendronate sodium. To the best of the firm's knowledge no extraordinary circumstances exist in regards to this action.

This sNDA is being provided in both paper copy and electronic format, with the exception of Items 11 and 12 (Case Report Tabulations and Case Report Forms), which are being provided in electronic format only (see attached "Statement of Organization").

This application is also being submitted electronically in accordance with the Guidance for Industry - Archiving Submissions in Electronic Format - NDAs, published September, 1997.

This sNDA is being submitted in the following formats:

<u>FORMAT</u>	<u>INFORMATION INCLUDED</u>	<u>MEDIA FORMAT</u>	<u>DATE OF SUBMISSION</u>
Paper	(all information except CRTs and CRFs)	Paper	January 28, 1999
Electronic Archival Files	sNDA Table of Contents, Case Report Tabulations, Case Report Forms	CD 	January 28, 1999
Electronic Submission	(all information)	CD	February 5, 1999 (to Technology Services Support Staff)

As noted in the Guidance document, this letter is being included as *cover.pdf* and includes:

- Appropriate regulatory information
- A description of the submission
- A description of which portions of the submission are presented only in paper, only in electronic format, or both paper and electronic format (*see above*)
- A description of the electronic submission including the contents of the media, their number and format, a description of the file types and the total size of the submission
The electronic archival files for Case Report Tabulations and Case Report Forms are provided on 1 CD. The files are provided in .PDF and .PDF catalogue index format. The total file size is approximately 193 MB.
- Verification that the submission is virus free with a description of the software used to check the files for viruses
Merck Research Laboratories (MRL) has employed Norton anti-virus (NAV) software and has scanned all files. No viruses were detected.
- A description of any deviation from the specifications in the guidance document
There are no deviations from the specifications as noted in the guidance document.

MRL will work with the FDA to arrange orientation to the electronic submission for all interested Agency reviewers.

Solomon Sobel, M.D., Director
NDA 20-560: FOSAMAX™ (Alendronate Sodium Tablets)
Page 3

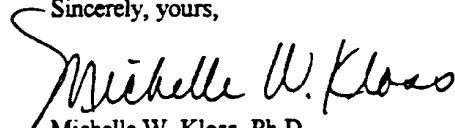
As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, Merck & Co., Inc., did not and will not use in any capacity the services of any debarred under sections 306(a) or (b) of the Act.

MRL would like to meet with the FDA approximately 90 days following receipt of this application. The purpose of this meeting will be to discuss the general progress and status of the review of this application and to determine if there are any important deficiencies identified at that time. MRL will contact the FDA to arrange for this meeting.

We consider the filing of this Supplemental New Drug Application to be a confidential matter and request that the Food and Drug Administration not make its content, nor any future communications in regard to it, public without first obtaining written permission from Merck & Co., Inc.

If you have any questions or need further information, please contact Michelle W. Kloss, Ph.D. (610/397-2905) or, in my absence, Larry P. Bell, M.D., (610/397-2310)

Sincerely, yours,



Michelle W. Kloss, Ph.D.
Director
Regulatory Affairs

Q:RCMK-0217EstrogenCOVER

Attachment

Hand Deliver

Desk Copy

Mr. Randy Hedin, HFD-510, Room 14B-04 - Federal Express #1

Desk Copy (Letter and Patent Information Only)

Ms. Mary Ann Holovac, HFD-93, 5600 Fishers Lane
Rockville, MD 20857 - Federal Express #2